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Is i.v. iron really superior in CKD patients not on dialysis?

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To the Editor: Van Wyck *et al.*[1] administered 1 g intravenous (i.v.) iron over the first 2 weeks, whereas oral iron was given over 8 weeks. As the rates of administration of iron were different, the appropriate comparison should be the proportion of patients achieving the primary end point at the end of 10–12 weeks and make the results more clinically relevant. In the analysis presented, it is assumed that patients who achieved 1 g/dl increase in hemoglobin at 2 weeks would also have the same response at 56 days. In the interest of intention-to-treat, the authors should also present the data for all patients randomized even when erythropoietin dose was not stable at baseline. The authors should be cautious in concluding that i.v. iron is safe in the long term. Progression of chronic kidney disease takes years and it would appear naive to declare safety of i.v. iron by reporting two estimated glomerular filtration rates over a course of 56 days! Notably, the improvement in hemoglobin with i.v. iron was only 0.3 g/dl more in the i.v. iron group, and 2/30 patients who received the high dose of 500 mg iron sucrose experienced severe hypotension sufficient to visit the emergency room. Thus, caution is warranted, when using high-dose i.v. iron. The authors measured C-reactive protein, yet do not report the data. Change in proteinuria was not reported and the multivariate logistic model for odds of hemoglobin response was also not presented as stated in the methods. These additional data would help interpret the results of this trial better.

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Response to Is i.v. iron really superior in CKD patients not on dialysis?

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Dr Agarwal[1] raises a number of important questions. The answer to the title question would seem to be yes, i.v. iron is superior to oral iron. Moreover, the degree of difference is clinically significant: in chronic kidney disease patients with anemia (hemoglobin (Hb) <11 g/dl) without erythropoiesis-stimulating agents (ESA) or without an increase in ESA dose, i.v. iron administration will raise the Hb higher, stimulate a Hb increase >1.0 g/dl more often, achieve or exceed the target Hb threshold of $\geqslant 11.0$ g/dl more consistently, and replete iron stores more reliably than oral iron therapy. The answer to whether we should have included patients with ESA dose increases in the analysis of efficacy is no. Increasing ESA doses, like starting ESA anew, administering additional i.v. iron off protocol, or transfusing the patient, introduces a co-intervention. The penalty for including co-interventions is the inability to isolate iron treatment effects. As we discussed, previous randomized controlled trials that failed to preclude co-interventions failed to show between-group differences in patients assigned to i.v. iron or oral iron treatment.[2,3]

Was the duration of the trial sufficient to show efficacy? We demonstrated that the peak Hb response in both treatment groups occurred before 42 days, well before completion of the 56-day observation period. Among patients assigned to oral iron, peak increase in Hb was lower than in i.v.-treated patients, as we showed, but time to peak increase did not differ between groups (Cox proportional hazards model: 36.1 vs 39.9 days, oral vs i.v.; $P=0.3481$). Logistic regression analysis yielded only baseline ferritin <100 ng/ml as a significant covariate in increasing the odds of a positive Hb response, a result we explored in more detail in the analyses we presented in Table 2.

Was the duration of the trial sufficient to conclude that i.v. iron, compared to oral iron, is safe in patients with chronic kidney disease? Three randomized controlled trials, including ours, have examined the effect of i.v. iron administration compared to oral iron therapy on renal function in chronic kidney disease patients. In the first, patients given i.v. iron sucrose 300 mg monthly up to 6 months showed a rate of decline of renal function no different from that seen in patients given oral iron.[2] In the second, patients assigned to oral iron therapy showed a significant decline in ClCr, whereas their counterparts given i.v. iron dextran 100 mg twice monthly up to 3 months showed no decline.[4] Our results in patients who received five 200 mg doses or two 500 mg doses of iron sucrose showed a slower rate of decline of glomerular

filtration rate in patients treated with i.v. iron compared to those assigned to oral iron therapy. Taken together, the evidence suggests that i.v. iron is at least as safe as oral iron in preserving glomerular filtration rate in anemic chronic kidney disease patients. We, as others,[2] found no effect of either i.v. iron or oral iron on C-reactive protein.

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